ABBOTT LABORATORIES

Corporate Regulatory and Quality Science

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October 2, 2000

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061
HFA-305
Rockville, MD 20852

RE: Docket: 00D-1418 - Q7a ICH Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients

To Whom It May Concern:

Abbott Laboratories is pleased to have the opportunity to provide comments on the revised draft guidance entitled "Q7a ICH Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients" published on July 19, 2000, in the *Federal Register*. In addition to this hardcopy, we have also used e-mail to propose the attached modifications to the text to help clarify some ambiguities.

On behalf of the 57,000 Abbott employees who help produce health care products marketed in more than 130 countries worldwide, we thank you for your consideration of our comments. Please contact Mr. Jody Voight, an employee of Abbott Laboratories, should you have any questions (phone 847-937-2841, or fax at 847-937-7369).

Sincerely,

D. L. Sporn

Douglas L. Sporn

cc: Jody Voight, Abbott Laboratories

Attachment

00D-1418 C1

ABBOTT LABORATORIES **October 2, 2000**

Comments to FDA

EXAMPLE

	Introduction
1.3	*Scope*
	The term "biotech" is used in the table of "Increasing GMP Requirements"
18.1	*Specific Guidance for APIs Manufactured by Cell Culture/Fermentation*
18.10	*In general, the degree of control for biotech processes is greater than for classical fermentation processes.*

DISCUSSION

The term "Biotech" is used throughout the document and in the introduction in regard to requirements. The term is open to interpretation because it is not defined within the document.

PROPOSED CHANGE

Provide a glossary definition for the term "biotech"

ABBOTT LABORATORIES **October 2, 2000**

Comments to FDA

EXAMPLE

Section 2	**Quality Management**
2.14	*Any deviation from established procedures should be documented and explained. Critical deviations should be investigated, and the investigation and its conclusions should be documented.*
2.22	*The main responsibilities of the independent quality unit(s) / should not be delegated. These responsibilities should be described in writing, and should include but not necessarily be limited to:* *4. Making sure that critical deviations are investigated and resolved;*
2.3	The responsibility for production 4. *Making sure that all production deviations are reported and evaluated and that critical deviations are investigated and the conclusions are recorded;*
8.15	*any deviation should be documented and explained. Any critical deviation should be investigated.*
11.15	*any deviation from [laboratory controls] should be documented and justified.*

DISCUSSION

The treatment of deviations is not consistent within the document.

PROPOSED CHANGE

Use consistent requirement in reference to deviations such as "investigated and justified."

Comments to FDA

EXAMPLE

5.4 **Computerized Systems**

5.47 *All changes to the computerized system should be made according to a change procedure and should be formally authorized, documented and tested.*
Records should be kept of all changes including modifications and enhancements made to the hardware, software and any other critical component of the system to demonstrate that the final system is maintained in a validated state.

DISCUSSION

The current wording will not allow for minor changes without formal authorization and testing. This level of change procedure may not be appropriate for minor changes.

PROPOSED CHANGE

All changes to the computerized system should be made according to a change procedure. Critical changes should be formally authorized, documented and tested. Records should be kept of all changes including modifications and enhancements made to the hardware, software, and any other critical component of the system to demonstrate that the final system is maintained in a validated state.

Comments to FDA

EXAMPLE

6.1 **Documentation System and Specifications**

6.14 *When entries need to be made in records, these should be made indelibly in spaces provided for such entries, directly after performing the activities (in the order performed), and should identify the person making the entry. Corrections to entries should be dated and signed and leave the original entry still readable.*

DISCUSSION

Statement "when entries need to be made in records...directly after performing the activities (in the order performed)..." "in the order performed" and be removed. The statement is redundant.

PROPOSED CHANGE

Remove the statement "in order performed."

ABBOTT LABORATORIES **October 2, 2000**

Comments to FDA

EXAMPLE

7.	**MATERIALS MANAGEMENT**
7.1	**General Controls**
7.12	*Materials should be purchased against an agreed specification, from a supplier or suppliers approved by the quality unit(s).*

DISCUSSION

The glossary definition of "specification" would imply that suppliers are required to test material per the manufacturers methodology. In some instances equipment or expertise may not be available to smaller suppliers to perform testing.

PROPOSED CHANGE

The term "specification" should be changed to "acceptance criteria."

ABBOTT LABORATORIES **October 2, 2000**

Comments to FDA

EXAMPLE

8. PRODUCTION AND IN-PROCESS CONTROLS
8.1 Production Operations
8.12 *Critical weighing, measuring, or subdividing operations should be supervised or subjected to an equivalent control. Prior to use, production personnel should verify that the materials are those specified in the batch record for the intended intermediate or API.*

DISCUSSION

The statement *"operators should be supervised..."* implies that a person of higher level must verify critical activities.

PROPOSED CHANGE

Change word "supervised" to witnessed or verified.

ABBOTT LABORATORIES **October 2, 2000**

Comments to FDA

EXAMPLE

8.3 **In-process Sampling and Controls**

8.32 *Critical in-process controls (and process monitoring), including the control points and methods, should be stated in writing and approved by the quality unit(s).*

DISCUSSION

The statement is not clear as written and may be interpreted that both critical in-process controls and all process monitoring must be stated in writing and approved by the quality unit(s).

PROPOSED CHANGE

Change statement to "critical in-process controls (and critical process monitoring)... should be stated in writing and approved by the quality unit(s)."

Comments to FDA

EXAMPLE

11. LABORATORY CONTROLS

11.1 General Controls

11.17 *Primary standards should be obtained as appropriate for the manufacture of APIs. The source of each primary standard should be documented. Records should be maintained of each primary standards storage and use in accordance with the supplier's recommendations. Primary reference standards obtained from an officially recognized source need not be tested if stored under conditions consistent with the supplier's recommendations.*

11.18 *In cases where a primary standard is necessary and one is not available from an officially recognized source, an "in-house primary standard" should be established. This standard may be prepared by independent synthesis or by further purification of existing production material. Appropriate testing should be performed to establish fully the identity and purity. Appropriate documentation of this testing should be maintained.*

11.19 *Secondary laboratory reference standards should be appropriately prepared, identified, tested, approved, and stored. The suitability of each batch of secondary reference standard should be determined prior to first use by comparing against a primary reference standard. Each batch of secondary reference standard should be periodically re-qualified in accordance with a written protocol.*

DISCUSSION

Companies should determine how a reference standard is prepared. "*This standard may be prepared by independent synthesis or by purification of existing production material*" may be too restrictive for production material which is of acceptable purity.

PROPOSED CHANGE

Change statement in 11.18 to "This standard may be prepared by independent synthesis or from existing production material of acceptable purity."

Comments to FDA

EXAMPLE

11.2 Testing of Intermediates and APIs

11.21 *An impurity profile describing the identified and unidentified impurities present in a typical batch produced by a specific controlled production process should normally be established for each API. The impurity profile includes the identity or some qualitative analytical designation (e.g. retention time), the range of each impurity observed, and classification of each identified impurity (e.g. inorganic, organic, solvent). The impurity profile is normally dependent upon the process and origin of the API. Impurity profiles are normally not necessary for APIs from herbal or animal tissue origin. Biotech considerations are covered in ICH Guideline Q6B.*

DISCUSSION "the range of each impurity observed" is vague for unidentified impurities for "classical fermentation" processes. Without appropriate standards, unidentified impurities may not be quantified since a response factor (HPLC) cannot be established.

PROPOSED CHANGE

There should be an option for including minor impurities in a "total unidentified impurities" specification (with a "largest single impurity" range specified), which is recognized in the major compendia.

Comments to FDA

EXAMPLE

11.22 *The impurity profile should be compared at appropriate intervals against the impurity profile in the regulatory submission or compared against historical data in order to detect changes to the API resulting from modifications in raw materials, equipment operating parameters, or the production process.*

DISCUSSION This should be modified to require an impurity profile (qualitative and quantitative) comparison against previously produced material (from the regulatory submission and/or validation documents) whenever a change is made to a critical process step.

ABBOTT LABORATORIES **October 2, 2000**

Comments to FDA

EXAMPLE

13. CHANGE CONTROL

13.15 *After the change has been implemented, there should be an evaluation of the first batches produced or tested under the change.*

DISCUSSION

The statement as written does not allow for minor changes which may not have an impact on product quality to be implemented without evaluation of the next batches.

PROPOSED CHANGE

Change to After major (or significant) changes that may impact the quality of the API, there should be an evaluation of the first batches produced or tested under the change.

Comments to FDA

EXAMPLE

14. REJECTION AND RE-USE OF MATERIALS
14.2 Reprocessing
14.21 *Continuation of a chemical reaction after an in-process control test shows the reaction to be incomplete is considered to be part of the normal process. This is not considered to be reprocessing.*

DISCUSSION

The example is very specific to chemical manufacturing, with reference to fermentation and biotech manufacturing within the document the example provided for reprocessing and the glossary definition should be more universal in nature.

PROPOSED CHANGE

Modify 14.21 to state "Continuation of a process step after an in-process control test shows the step to be incomplete is considered to be part of the normal process. This is not considered to be reprocessing.

20. GLOSSARY
Reprocessing-...continuation of a ~~chemical reaction~~ process step after an in-process control test...

Comments to FDA

Example

18. **SPECIFIC GUIDANCE FOR APIS MANUFACTURED BY CELL CULTURE/FERMENTATION**

18.3 **Cell Culture/Fermentation**

18.33 *Critical operating parameters, for example temperature, pH, agitation rates, addition of gases, pressure, should be monitored to ensure consistency with the established process. Cell growth, viability (for biotech processes), and productivity should also be monitored. Critical parameters will vary from one process to another, and for classical fermentation certain parameters (cell viability, for example) may not need to be monitored.*

DISCUSSION

The use of the word critical, as defined in the glossary, would imply specifications. Unqualified, the statement implies that there are critical parameters in every case. As written, the use of the word critical suggests that every fermenatation process has a critical parameter that would require specifications in addtiion to basic control. In some instances, classical fermentation processes are essentially a "go/no-go" event where only the production of the API, or API starting material, is important to the process.

PROPOSED CHANGE

Reword "Critical operating parameters..." to "Operating parameters that have been determined to be critical to the quality of the API..."

Comments to FDA

EXAMPLE

19. APIS FOR USE IN CLINICAL TRIALS

DISCUSSION

The document makes reference to clinical material however does not difine this term in the glossary

PROPOSED CHANGE

Include definition of clinical material in glossary. "Clinical APIs - APIs used in drug products intended for clinical trials in human use only."

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